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An Open Trial of Citalopram in Children and Adolescents with Depression

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ABSTRACT

Objective: **The aim of this study was to collect pilot data on the magnitude of effect and tolerability of citalopram in early-onset major depressive disorder (MDD).**

Method: **This study was performed in two academic child and adolescent psychiatric clinics (2000 through 2002). Thirty children and adolescents, 8–17 years of age (mean age, 13.57 ± 2.5), of both sexes (53.3% girls; 46.7% boys) and diagnosed with MDD by means of clinical psychiatric evaluation, Diagnostic Interview for Children and Adolescents (DICA) and the *Diagnostic and Statistical Manual of Mental Disorders*, 4th edition (DSM-IV) criteria, were studied in an open-label clinical trial with 10–40 mg/day of citalopram for 6 weeks. The outcome measures were the Hamilton Depression Rating Scale (HDRS), the Children Global Assessment Scale (CGAS), and the New York State Psychiatric Institute side-effect form.**

Results: **Moderate (50%–70% change in HDRS and CGAS) to large (> 70% change in HDRS and CGAS) effect were seen in 91.7% of children (22/24). There were significant changes on HDRS (X = 22.78; t = −14.12; $p < 0.000$) and CGAS (X = 26.02; t = 9.68; $p < 0.000$) between baseline and the 6th week. Mild side effects were reported in 2 patients (8.3%). Adverse effects that contributed to discontinuation were nausea and vomiting in 3.3% ($n = 1$) of patients and unexpectedly switching to mania in 16.7% ($n = 5$) of patients.**

Conclusion: **Citalopram may be an efficatious treatment in early-onset MDD. However, the high switch rate to mania warrants further investigations, as well as cautions, in using it.**

INTRODUCTION

Early-onset (under 18 years of age) major depressive disorder (MDD) is a common and recurrent illness (Birmaher et al. 1996). The prevalence of MDD ranges between 0.4% and 2.5% in children and between 0.4% and 8.3% in adolescents (Fleming and Offord 1990; Kashani et al. 1987a,b; Lewinsohn et al. 1994). Depression in adults often begins in adolescence (Kessler et al 1994; Lewinsohn et al. 1993a,b). Children and adolescents with clinical depression have high morbidity and mortality rates (Birmaher et al. 1996). They experience impairment in school performance and relationships with others (Kovacs 1996; Kovacs et al. 1997; Puig-Antich et al. 1993; Rohde et al. 1994). Depression in children and adolescents contributes to increased risk for suicidal behavior, homicide, tobacco use, and substance abuse during later adolescence

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and adulthood, compared to individuals without early-onset depression. They are at high risk for physical illness, early pregnancy, exposure to negative life events, and poor work performance, as well as academic and psychosocial functioning (Birmaher et al. 1996; Kovacs 1996; Kovacs et al. 1997). There is also a secular increase in the prevalence of MDD, and it appears that it is occurring at an earlier age in successive cohorts, underscoring the necessity for early identification and prompt treatment interventions (Kovacs and Gatsonis 1994; Ryan et al. 1992).

Controlled, double-blind trials have reported no significant differences between placebo and tricyclic antidepressants (TCAs), reporting a 40%–60% response rate to both (Hughes et al. 1990; Kashani et al. 1984; Petti and Law 1982; Puig-Antich et al. 1987). Selective serotonin reuptake inhibitors (SSRIs) are efficacious for the treatment of adults (Thase and Kupfer 1996) and youths (Emslie et al. 1997) with MDD. They have a relative benign side-effect profile, very low mortality after an overdose, and suitability for long-term maintenance (De Vane and Sallee 1996; Kutcher 1997; Leonard et al. 1997; Preskorn 1994). In open studies, 70%–90% of adolescents with MDD show a treatment response to SSRIs (De Vane and Sallee 1996; Leonard et al. 1997; Rey-Sanchez and Gutierrez-Casares 1997). An 8-week, double-blind, placebo-controlled trial of fluoxetine in 96 children and adolescents with nonpsychotic MDD showed significantly better response to fluoxetine than placebo (56% versus 33%), with 31% achieving full remission (Emslie et al. 1997). Citalopram, which is the most selective SSRI, is indicated for treatment of depression in several countries (Keller 2000). Double-blind, placebo-controlled studies have proven the efficacy of citalopram in treating MDD in adults (Montgomery et al. 1993; Mendels et al. 1999). Compared to the TCAs, citalopram shows a superior side-effect profile and a more rapid onset of action (Shaw et al. 1986). It has several potential advantages over other SSRIs. It is reported to have fewer side effects (Baldwin and Johnson 1995) and lesser drug reactions than other SSRIs (Greenblatt et al. 1998; Montgomery 1998; Nemeroff et al. 1996; Keller et al. 2001). There have been a few studies evaluating citalopram's efficacy in children and adolescents with MDD (Baumgartner et al. 2002; Bostic et al. 2001). Our study was designed to collect preliminary data on the effectiveness and tolerability of citalopram in children and adolescents with MDD.

METHOD

Subjects were children and adolescents (under 18 years of age) of both genders who were admitted to the child and adolescent psychiatric clinics of Roozbeh and Iran hospitals (two referral centers affiliated with Tehran and Iran University) during 2000–2002.

To be included in this study, subjects had to meet criteria of the *Diagnostic and Statistical Manual of Mental Disorders*, 4th edition (DSM-IV) for major depressive disorder (MDD), had to be in good medical health, and had to have normal intelligence. In addition to a structured psychiatric interview, the initial evaluation included a medical review of systems, a physical and neurological examination, electroencephalography (EEG) (to exclude seizure disorders), electrocardiography (ECG), and laboratory tests (complete blood-cell and differential-cell count, urinalysis, thyroid function tests, liver function tests, fasting blood sugar, cholesterol, triglyceride, blood urea nitrogen, and creatinine). They were screened for other psychiatric disorders, using the Diagnostic Interview of Children and Adolescents (DICA). Diagnosis was made by a certified child and adolescent psychiatrist, based on information from interviews of the parent and child.

Exclusion criteria were all known organic pathologies presenting with depressive or confounding symptoms. A full-scale IQ below 70 (mental retardation) was excluding as well. Two subjects were not enrolled in the study because of organic pathologies, which were grand mal epilepsy in one of the subjects and minor thalasemia in the other. Written, informed consent and assent to participate in the study were obtained from parents and corresponding patients.

Before entering the study, any subjects on psychotropic medications were required to discontinue them for at least 2 weeks before the study began.

Depressive symptom severity was assessed using the Hamilton Depression Rating Scale (HDRS) because it is available in Farsi. Overall, functioning was assessed using the Children's Global Assessment Scale (CGAS). The New York State Psychiatric Institute side-effect form for clinical trial in children and adolescents was used to assess medication side effects.

The treatment phase of this study consisted of a 6-week, open label medication trial after a 2-week washout period for subjects previously on psychotropic medications. The duration of 6 weeks is one of the recommended durations for open clinical trials in children and adolescents with depression (Klein et al. 1994). Citalopram was initiated at 10–20 mg per day in the morning determined by clinician's judgment. The medication was prescribed by the psychiatrist, and the dosage was adjusted on an individual basis at 10–40 mg per day. The dose schedule was designed to be stabilized by week 6. Compliance was evaluated by pill count.

The psychiatrist maintained weekly contacts (or more, if indicated) with the subjects and/or parents. At these times, weekly ratings of HDRS, CGAS, side-effect form, and pill count were completed. Detailed progress notes were recorded after each visit as well.

A paired *t* test was applied to compare the pre- and posttreatment ratings. A p value of <0.05 was chosen to represent statistical significance.

Table 1. Clinical Characteristics of MDD Sample

*Features (*N = *30)*	
Demographic	
Age, year range	8–17
Age, mean (±SD)	13.57 (±2.5)
Female, N(%)	16 (53.3%)
Male, N(%)	14 (46.7%)
Primary school, N(%)	6 (20%)
High school, N(%)	24 (80%)
Clinical	
Inpatient, N(%)	9 (30%)
Outpatient, N(%)	21 (70%)
Comorbid Diagnoses	
Obsessive-compulsive disorder, N(%)	13 (43.3%)
Simple phobia, N(%)	9 (30%)
Generalized anxiety disorder, N(%)	5 (16.7%)
Oppositional-defiant disorder, N(%)	3 (10%)
Tic disorder, N(%)	2 (6.7%)
Attention-deficit/hyperactivity disorder, N(%)	2 (6.7%)

MDD, major depressive disorder; N, number of patients; SD, standard deviation.

RESULTS

Of the initial 30 subjects, 24 subjects completed the study. Demographic, clinical characteristics and comorbid diagnoses of the sample are summarized in Table 1.

The average daily dose of citalopram was 20.8 mg, with a range of 10–40 mg per day. At the end of the study, 2 subjects (8.3%) were taking 10 mg per day, 20 subjects (83.3%) were taking 20 mg per day, and the other 2 subjects (8.3%) were taking 40 mg per day.

Therapeutic effects

Table 2 and Figure 1 show responses to medication from baseline through week 6. There were significant changes on outcome measures between baseline and 6 weeks of treatment with citalopram. None of the subjects met criteria for MDD at the end of the study.

Table 3 summarizes the range of changes in HDRS and CGAS. As Table 3 shows, moderate (50%–70%) to large (> 70%) improvements are seen in 91.7%.

Adverse effects

No statistically significant changes were found in weight, height, or vital signs. Three subjects (10%) reported mild side effects, which resolved spontaneously or with dosage adjustment. They were delayed menstrual period, diuresis, nausea, and diaphoresis. Physical side effects, as a reason for discontinuation, occurred in only 1 patient who developed gastrointestinal complications; mainly, nausea and vomiting. No suicidal thoughts or behaviors were reported in the sample during the study.

Five patients (16.7%) discontinued the medication because of their switching to mania, which was significantly high. They were 3 boys and 2 girls with a mean age of 12.6 (±1.92) years. All of the patients were experiencing their first episode of depression and 1 patient had obsessive-compulsive disorder and tic disorder as a

TABLE 2. MEAN AND STANDARD DEVIATION (SD) SCORES OF MDD SAMPLE BEFORE AND AFTER 6 WEEKS TREATMENT OF CITALOPRAM

	Baseline (N = 30)		*Six weeks paired T test (N = 24)*				
Measure	*Mean score*	*SD*	*Mean score*	*SD*	*df*	t-*score*	p-*value*
HDRS	32.9	±8.4	10.12	±7.5	23	−14.12	<0.000
CGAS	39.9	±8.4	65.92	±12.3	23	9.68	<0.000

HDRS, Hamilton Depression Rating Scale; CGAS, Children Global Assessment Scale; MDD, major depressive disorder.

comorbidity. They were taking 20 mg of citalopram per day from the beginning of the study and showed a full manic picture during the 2nd week.

All subjects who completed the study intended to continue the medication, although the high cost of medication was a major concern.

DISCUSSION

Citalopram treatment was effective in relieving early-onset depressive symptoms, and this was evident in CGAS and HDRS. Differences before and 6 weeks after the onset of treatment were statistically significant on both scales.

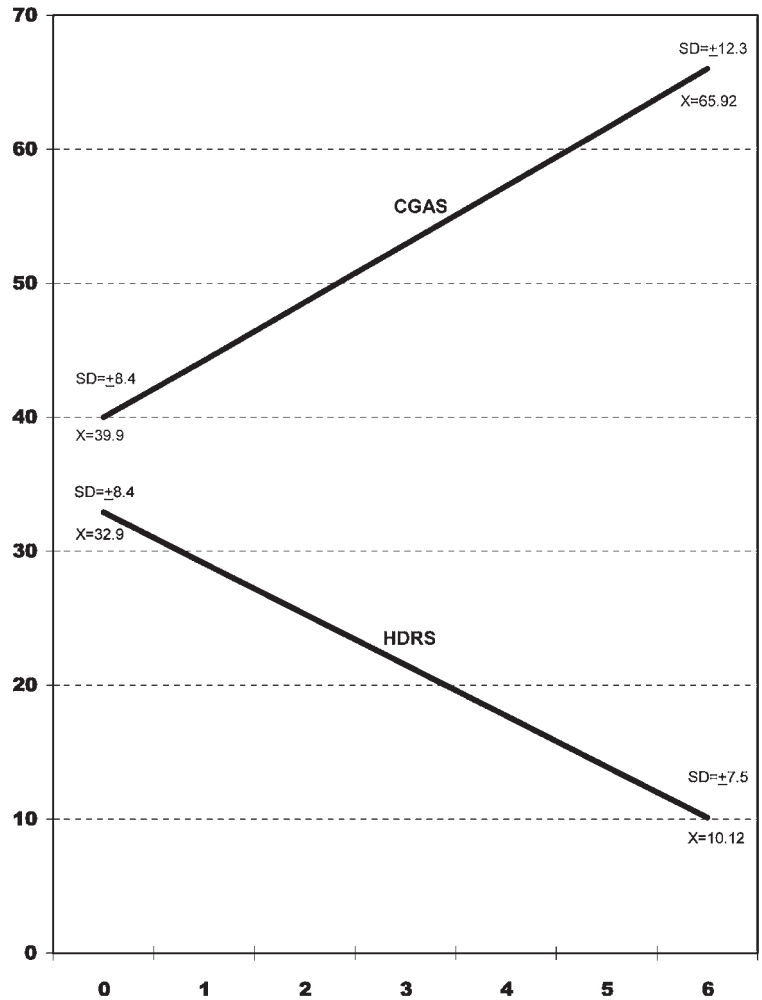

FIG. 1. Mean (X) and standard deviation (SD) of HDRS and CGAS scales before and after 6 weeks treatment of citalopram.

TABLE 3. CHANGE IN CGAS AND HDRS SCALES IN THE MDD SAMPLE AFTER 6 WEEKS OF TREATMENT WITH CITALOPRAM

	Range of change		
Measure	*< 50% Number of patients (%)*	*50%–70% Number of patients (%)*	*> 70% Number of patients (%)*
HDRS	2 (8.4%)	8 (33.3%)	14 (58.3%)
CGAS	2 (8.4%)	2 (8.3%)	20 (83.3%)

HDRS, Hamilton Depression Rating Scale; CGAS, Children Global Assessment Scale; MDD, major depressive disorder.

There was no clear difference in patient responsiveness based on age or gender. When reviewing the weekly ratings in this study, it was noted that most subjects showed improvement within 1–2 weeks after the onset of medication, consistent with adult studies comparing citalopram to other SSRIs, such as fluoxetine (Patris et al. 1996) and sertraline (Stahl 1998).

Citalopram has little or no affinity for pre- or postsynaptic receptors, such as those for dopamine, norepinephrine, and histamine (Hyttel et al. 1995). There are fewer complaints of side effects reported with citalopram use in other studies (Baldwin and Johnson 1995). In our study, where subjects took between 10 to 40 mg per day of citalopram, most adverse effects were minimal and tended to resolve spontaneously. There were no changes in vital signs as well. However, our finding of a high switch rate from depression to mania is alarming. Follow-up studies have found that 20%–40% of children and adolescents with MDD develop bipolar I disorder within a period of 5 years after the onset of depression, and early-onset depression is associated with an increased risk of developing bipolar I disorder (Geller and Luby 1997; Kovacs et al. 1997; Kovacs 1996; Strober et al. 1995; Strober and Carlson 1982). Many youth referred for depression are experiencing their first depressive episode. Because the symptoms of unipolar and bipolar depression are similar, it is difficult to determine whether a patient needs only an antidepressant or concomitant use of mood stabilizers. Some patients have to discontinue the treatment because of switching to mania.

Limitations

As comorbid disorders were frequent, measurements assessing other symptoms—not only depression—might change differentially as a function of treatment. The number of patients in this study, however, did not allow evaluating the responses according to coexisting disorders. Future studies should take this into account by examining subgroups.

Because of the limited duration in this study (6 weeks), there may be an uncertainty whether gains were stable. In addition, placebo effects could have added to the effects observed.

CONCLUSION

The findings of this study suggest that citalopram, at 10 to 40 mg per day, may be efficatious in acute-phase treatment of MDD in children and adolescents. However, adverse side effects are of concern. Our findings are relevant to clinicians who are faced with treatment decisions for early-onset depression and a relative limited data guiding therapeutic choice. Prospective double-blind, controlled studies involving placebo and other drug comparisons in larger samples and longer durations are warranted to confirm these findings.

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